REMARKS

Claims 1-4, 6-11, 14, 16-18, 22, 23, and 33-47 are pending; claims 5, 12, 13, 15, 19-21, and 24-32 have been cancelled; and claims 33-47 are new. Claim 1 has been amended. No new matter has been introduced by way of the amendments to the claims.

Applicants note that they have amended claim 1 in this response and in the responses filed August 10 and September 2 simply to comply with the Restriction Requirement mailed December 9, 2008. Group I of the Restriction Requirement requires that "neither R nor R' are cyclic and R_1 and R_2 do not form a heterocycle with the nitrogen to which they are attached." (Emphasis in the original). Accordingly, Applicants deleted the group "heterocycloalkyl" from R' and the recitation that R_1 and R_2 could "form together with the nitrogen atom to which they are attached an optionally substituted heterocycle." At the in-person interview described below, Examiner Zarek indicated that, to comply with the Restriction Requirement, the group "aryl," which admittedly is cyclic, had to also be removed from the definition of R'.

I. *Examiner Interview*

The undersigned and the Applicants wish to thank Examiners Zarek and Hui for the cordial and productive interview of August 27, 2009. The Examiner's helpful comments and suggestions were instrumental in preparing this response. During the interview, Applicants' representatives discussed the rejection under 35 U.S.C. § 112, first paragraph (enablement) and claim amendments that may overcome that rejection. Applicants' representatives also discussed that the claimed invention is patentable over the art of record.

II. *Priority*

On page 3 of the Office Action, the Patent Office states that "Applicant has not properly claimed the benefit of the prior -filed international application," namely PCT/FR05/000713. The Patent Office States that in order to claim that benefit, "[t]he later-filed application must contain a reference to the prior-filed application in the first sentence(s) of the specification or in an application data sheet, for a benefit claim under 35 U.S.C. 120, 121, or 365(c), and also for a benefit claim under 35 U.S.C. 119(e)." Applicants assert that they have properly and timely claimed the benefit of PCT/FR05/000713 as shown in the attached copy of the Official Filing receipt (Exhibit A) mailed July 29, 2008.

III. *The rejection under 35 U.S.C. § 112, first paragraph should be withdrawn*

Claims 1-4, 6-19, 21, 23, 25-28, and 32 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement for the reasons set forth on pages 3-7 of the Office Action. The Patent Office has concluded that it would require undue experimentation to use the invention as claimed. While not acquiescing to the Patent Office's position regarding the enablement of a claim directed to the prevention and/or treatment of hearing loss, and simply in an effort to advance the prosecution of the instant application, Applicants have amended claim 1 such that it is directed to a method for protecting acoustic hair cells by administering the claimed compounds. The Experiments described in the instant application show that the compounds protect acoustic hair cells and either prevent significant hearing loss or restore hearing. *See, e.g.*, ¶[0072] and ¶¶[0090]-[0097] of the published application. Even if the Patent Office is of the opinion that a claim directed to the prevention and/or treatment of hearing loss at any time before or after the hearing loss is not enabled, a claim directed to a method for protecting acoustic hair cells is clearly enabled. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

To the extent that this rejection could apply to new claims 33-47, Applicants assert that new claim 33, which is directed to a method of treating hearing loss comprising administering, up to 24 hours following an acoustic traumatism, a heterocyclic derivative of formula (I), is enabled. *See, e.g.*, Experiments at ¶¶[0090]-[0097] of the published application showing that the compounds restore hearing. The Patent Office, in fact, admits that such a claim is enabled. *See* Office Action mailed February 9, 2009 at page 4.

IV. *The rejection under 35 U.S.C. § 112, second paragraph should be withdrawn*

Claims 14 and 21 stand rejected under 35 U.S.C. § 112, second paragraph for the reasons set forth on page 7 of the Office Action. Applicants assert that this rejection is moot with respect to claim 21 because that claim was cancelled. In addition, the rejection of claim 14 is overcome by the amendment to claim 14. Specifically, claim 14 was previously amended to incorporate the features of claim 15. Reconsideration and withdrawal of the rejection of claims 14 and 21 under 35 U.S.C. § 112, second paragraph are respectfully requested.

Claim 22 stands rejected under 35 U.S.C. § 112, second paragraph for the reasons set forth on pages 7 and 8 of the Office Action. Applicants assert that this rejection is overcome by

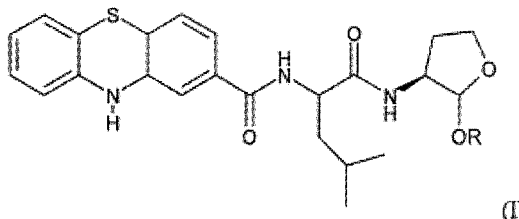
the amendments to claim 22. Specifically, claim 22 was previously amended to convey that the other substance with pharmaceutical activity is administered in an additional step of the claimed method. Applicants wish to point out that the other substance with pharmaceutical activity can be administered before, after or together with a compound of formula (I). Since the step recited in claim 22 represents an additional step, Applicants assert that there need not be antecedent basis for the additional step in claim 22. Applicants therefore request reconsideration and withdrawal of the rejection of claim 22 under 35 U.S.C. § 112, second paragraph.

Claims 12 and 13 stand rejected under 35 U.S.C. § 112, second paragraph for the reasons set forth on page 8 of the Office Action. Applicants respectfully assert that this rejection is moot in view of the cancellation of claims 12 and 13. Reconsideration and withdrawal of the rejection of claims 12 and 13 under 35 U.S.C. § 112, second paragraph are therefore respectfully requested.

V. *The rejection under 35 U.S.C. § 103(a) should be withdrawn*

Claims 1-4, 6-23, 25-28, 30, and 32 stand rejected under 35 U.S.C. § 103(a) over Seidman in view of Takumida, et al. and Auvin, et al. for the reasons set forth on pages 9-11 of the Office Action. Applicants respectfully traverse this rejection.

The instant invention relates to a method of protecting acoustic hair cells and to a method for treating hearing loss comprising administering a heterocyclic derivative of formula



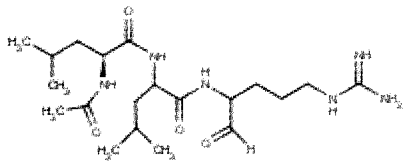
(I)

diastereoisomers of derivative (I), or combinations thereof, where the group R is defined above.

Seidman relates to the role of antioxidant in the protection of age-related hearing loss (i.e., presbyacusis). The studies described in Seidman "demonstrate that long-term treatment with compounds that either block or scavenge reactive oxygen metabolites [(ROMs)] have a protective effect on age-related hearing loss and the associated alterations at the genomic level." Seidman at 728, col. 1, lines 2-6. The types of compounds that Seidman studied are vitamin E,

vitamin C, melatonin, and lazaroids. *Id.* at page 730, col. 2, line 20 to page 731, col. 1, line 12. None of these compounds bear any relation to the presently claimed phenothiazines.

Takumida teaches that compounds such as the specific calpain inhibitor leupeptin may be useful to protect from gentamicin ototoxicity. Leupeptin has the following structure:



It is clear that leupeptin bears no relation to the presently claimed phenothiazines.

Finally, Auvin describes and claims phenothiazine compounds that have both calpain inhibitory activity, as well as antioxidant activity. Auvin, however, makes no mention of the use of those phenothiazines, or any of the disclosed compounds for that matter, for preventing or treating hearing loss, let alone for protecting acoustic hair cells. Instead, Auvin focuses on treating diseases including "inflammatory and immunological diseases, cardiovascular and cerebrovascular diseases, disorders of the central or peripheral nervous system, osteoporosis, muscular dystrophy, proliferative diseases, cataracts, organ transplants, auto-immune and viral diseases, cancer, and all pathologies characterized by an excessive production of ROS's and/or the activation of calpains." Auvin at 17:44-60.

Applicants assert that the combined teachings of Seidman, Takumida, and Auvin do not render obvious the original claims (preventing or treating hearing loss), the amended claims (protecting acoustic hair cells) or the new claims (treating hearing loss). The combined teachings of Seidman, Takumida, and Auvin do not even make it "obvious to try" to use Auvin's phenothiazines to treat hearing loss or to protect acoustic hair cells. This is because even after the Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.*, for something to be "obvious to try" "there [must be] a design need or market pressure to solve a problem and there [must be] a finite number of identified, predictable solutions [for solving that problem]." *KSR Int'l Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d 1385, 1397. Applicants assert that in the instant case, while there may be

market pressure to solve the problem of treating or preventing hearing loss or protecting acoustic hair cells, the number of solutions to that problem are potentially endless. For example, one could use Seidman's vitamin E, vitamin C, melatonin, or lazaroids. Or one could use Takumida's leupeptin or the other unnamed calpain inhibitors that Takumida references on page 12, col. 1, lines 2-4. Or, finally, one could use Auvin's phenothiazines, chromenes, diphenylamines, etc. But, even though Auvin identifies the disclosed phenothiazines and other various compounds as calpain inhibitors and antioxidants, he uses those compounds to treat a myriad of diseases, none of which are related to treating or preventing hearing loss. Accordingly, Applicants assert that it would not have been obvious to try to use Auvin's phenothiazines to treat hearing loss or to protect acoustic hair cells.

In addition, there simply is no reason, and the Patent Office has not provided one, why the skilled artisan would specifically use phenothiazines to treat or prevent hearing loss, let alone a reason to use phenothiazines to protect acoustic hair cells. In *KSR* the Supreme Court has stated that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does." *KSR Int'l Co.* 82 U.S.P.Q.2d at 1396. "To facilitate review, this analysis should be made explicit." *Id.* The obviousness rationale addressed in *KSR* was premised on combining elements known in the prior art. A parallel analysis applies, however, to a rejection premised on the obviousness of modifying a known method of treatment of diseases that have nothing to do to with treating or prevent hearing loss, such as Auvin's, thereby arriving at the claimed method. The *KSR* Court noted that obviousness cannot be proven merely by showing that the elements of a claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed." *Id.* Accordingly, since there doesn't appear to be a reason, and the Patent Office has not provided one, why the skilled artisan would specifically use phenothiazines to treat or prevent hearing loss, let alone for protecting acoustic hair cells, the obviousness rejection should be withdrawn. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Finally, Applicants ask the Patent Office to reconsider and withdraw the obviousness rejection in light of the following results that could not be predicted from the teachings of Auvin.

In the article submitted herewith, authored by three out of the five named inventors of the instant invention, it was found that two compounds that fall under the genus claimed in claim 1 achieved 100% cell protection. In contrast, a combination of a potent calpain inhibitor and an antioxidant, at best, achieved 66% cell protection. B. Pignol, *et al.*, "Calpain inhibitors and antioxidants act synergistically to prevent cell necrosis: effects of the novel dual inhibitors (cysteine protease inhibitor and antioxidant) BN 82204 and its pro-drug BN 82270," *Journal of Neurochemistry 98*: 1217-1228 (2006) (hereinafter "Pignol"; attached as Appendix A); *see* Fig. 6 on page 1223.

As shown in Fig. 5 of Pignol, 2-methoxy-10H-phenothiazine (an antioxidant) alone exhibits less than 10% protection and Z-Leu-Phe-H (a calpain inhibitor) alone, exhibits about 15% cell protection. The combination of 2-methoxy-10H-phenothiazine and Z-Leu-Phe-H shows about 40% cell protection. As shown in Fig. 6, the combination of BHT (an antioxidant) and Z-Leu-Leu-H (a calpain inhibitor) only achieved 66% cell protection. But, compounds BN 82204 (compound of claim 1, wherein R = H) and BN 82270 (compound of claim 1, wherein R = $C(O)CH_3$) both achieved 100% cell protection. Applicants assert that the results observed with the two compounds that fall under the genus claimed in claim 1 could not be predicted from the teachings of Auvin. For at least this additional reason, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

CONCLUSION

In view of the above remarks, early notification of a favorable consideration is respectfully requested.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Dated: September 14, 2009 By: _____

Robert M. Schulman
Registration No. 31,196

Ricardo J. Moran
Registration No. 48,735

Hunton & Williams LLP
Intellectual Property Department
1900 K Street, N.W., Suite 1200
Washington, D.C. 20006-1109
(202) 955-1500 (telephone)
(202) 778-2201 (facsimile)